Please amend claim 25 to read as follows:

36 25. (Once Amended) The conjugate of Claim 1 wherein the PEG molecule is covalently attached to the hinge region of the antibody fragment.

Please amend claim 26 to read as follows:

37 26. (Once Amended) The conjugate of Claim 1 wherein the antibody fragment comprises an antigen binding site that binds to human interleukin-8 (IL-8).

Please add the following new claim:

--36. (New) A conjugate consisting essentially of a Fab' fragment, attached to a single-chain polyethylene glycol (PEG) molecule of at least 20 kD, wherein said conjugate has an apparent size of at least about 500 kD and at least about 8 fold greater than the apparent size of at the antibody fragment.--

38

Remarks/Arguments

The foregoing amendments in the claims are fully supported by the specification as originally filed, and do not add new matter. All amendments, including cancellation of claims, have been done without prejudice, solely to facilitate the prosecution of the present application, and without acquiescence in any of the rejections. Applicants specifically retain the right to pursue subject matter within the full scope of the original claims in one or more continuing applications. Attached hereto is a marked-up version of the pages containing the foregoing amendments. The attached sheets are captioned "**Version with Markings to Show Changes Made**."

For the Examiner's convenience, in the following remarks and arguments, reference is made to the numbers used in the Office Action.

1. In response to the Examiner's suggestion to add a claim drawn solely to the elected species, claim 36 has been added. Applicants note that they understand the election of a

20 kD single-chain PEG molecule to be an election of species. Accordingly, should the species found to be patentable, applicants will be entitled to a genus claim encompassing a reasonable number of additional species. Accordingly, claims directed to other PEG species have not been canceled.

2. Applicants note that the Examiner recognized the January 22, 1998 as the effective filing date for all claims pending.

3. The title of the invention was found to be non-descriptive. The new title added by the foregoing amendment is in line with the Examiner' suggestion.

4. The specification has been amended to conform to the approved formal drawings.

5. The Examiner requested Applicants to re-supply the non-patent references listed in the Information Disclosure Statement filed on November 29, 2000. It is noted that all references cited in that Information Disclosure Statement have since been refined in connection with Application Serial No. 09/234,182 on October 17, 2002, and should be available to the Examiner. Should the Examiner have no access to the references, Applicants are ready to refile them, again, but would prefer to avoid the associated expenses, in view of the large number of references.

6. The specification has been checked for typographical errors, and the reference to the address of ATCC has been corrected.

7-8. Claims 1, 5, 6, 10-19, 21, 24-26, and 28-35 have been rejected as "indefinite" in their recitation of the term "consisting essentially of," because, according to the rejection, this term "is considered indefinite when used with a compound rather than a composition."

Applicants respectfully disagree and traverse the rejection as it applies to the currently pending claims. Although the phrase "consisting essentially of" typically precedes a list of ingredients in a composition claim, or a series of steps in a process claim, applicants are not aware of any case law that would outrule, or hold indefinite, the use of this phrase in a compound claim under appropriate circumstances. Indeed, the compound claimed in the present case is a conjugate, which includes the covalent attachment of a PEG molecule to an antibody Fab' fragment. Under these circumstances, one would understand that the term "consisting essentially of" means that the conjugate necessarily includes the Fab' fragment and the PEG molecule(s) attached to it, but might additionally have some modifications that do not materially affect the

basic and novel properties of the claimed conjugates. See, also *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351 (Fed. Cir. 1998) for discussion of the overall meaning of the term "consisting essentially of."

In view of these arguments, the Examiner is respectfully requested to withdraw the present rejection, or to cite supportive case law.

9. Applicants note the Examiner's reading of the term "apparent size."

10-11. Claims 1, 5, 8, 10-19, 21, 26, and 28-35 have been rejected under 35 USC § 112, first paragraph for alleged lack of enablement. The rejection, as it applies to the pending claims is respectfully traversed.

According to the rejection, the Examiner questioned the enablement for any antibody fragment linked to any nonproteinaceous polymer, and including more than one nonproteinaceous molecules. Without acquiescence in the rejection, and merely to facilitate the prosecution of the present application, the claims are now directed to Fab' fragments covalently attached to one PEG molecule, therefore, the reasoning underlying the rejection no longer applies. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

12-15. Claims 1, 5, 8, 10-19, 21, 24-26, and 28-35 have been rejected under 35 U.S.C. 102(e) as "being anticipated by Gonzalez et al. (U.S. Patent No. 6,133,426, see entire document). The attached Declarations under 37 CFR § 1.132 by Leonard Presta and Steven Leong, which were first submitted in parallel application Serial No. 09/234,182 establish that the cited patent is not "by another." Accordingly, the withdrawal of the present rejection would be in order.

16-17. Claims 1, 5, 8, 10-19, 21, 24-26, and 28-33 have been rejected under 35 USC § 103(a) "as being unpatentable" over Zapata et al. in view of Braxton (U.S. Patent No. 5,766,897).

The cited Zapata *et al.* reference is an Abstract of a poster presentation at a FASEP meeting in 1995. The poster presentation itself has been submitted by applicants with an Information Disclosure Statement, as Reference #109. The Zapata *et al.* poster presentation teaches that the nonspecific clearance of an antibody Fab fragment with a molecular weight of 49 kD can be decreased as much as 6-fold by the site-directed addition of a 10kD PEG moiety. The Zapata *et el.* poster presentation further teaches that as long the effective molecular size is below

70 kD, clearance decreases as molecular weight increases. Citing Knauf, *J. Biol. Chem.* 263:15064-15070 (1988) (Reference # 79 of record), Zapata *et al.* notes that this might not apply to molecular sizes that exceed the glomerular filtration cutuff size of 70 kD.

Indeed, Knauf *et al.* teach that the *in vivo* clearance rate of an PEG-rIL conjugate rapidly decreases as the effective molecular size increases from 21 to approximately 70 kD, but above 70kD clearance decreases much more slowly. Knauf *et al.* observed no further decrease in clearance rates when the apparent molecule weight of the protein was increased above 200 kD. In view of this teaching, one could not extrapolate from Zapata *et al.*'s data, which were obtained with less than 70kD antibody-PEG conjugates, that the clearance of antibody-PEG conjugates with an apparent molecular weight of at least about 500 kD would be reduced significantly. A person skilled in the art would not be motivated, based on the Zapata *et al.* poster presentation, and further in view of Knauf *et al.* to make and use antibody-PEG conjugates with apparent molecular weights of at least about 500 kD. Such increase of molecular weight would offer no further benefits over conjugates of smaller size, which are below the glomerular cutoff size.

Braxton *et al.* has no teaching that would make up for the deficiency of the primary reference. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection as it applies to the claims pending.

18. Claims 26 and 28 were rejected under 35 USC § 103(a) as allegedly obvious over Zapata et al., in view of Braxton et al., and further in view of Doerschuk et al. (U.S. Patent No. 5,702,946). Zapata et al. and Braxton et al were cited as discussed above. Doerschuk et al. was cited for its disclosure of anti-IL-8 antibodies, their humanized Fab' fragments, and other disclosure related to anti-IL-8 antibodies.

As discussed in response to the previous rejection, the combination of Zapata et al. and Braxton et al. does not make obvious the invention claimed in the claimed on which claims 26 and 28 depend. Since Doerschuk et al. does not make up for the deficiencies of the primary combination, claims 26 and 28 are non-obvious for the same reasons as the base claims on which they depend. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

19. Claims 34 and 35 were rejected under 35 USC § 103(a) as allegedly obvious over Zapata et al. in view of Braxton et al., and further in view of Griffith et al. (U.S. Patent No.

5,670,132). The first two references were cited as discussed above. Griffith et al. was cited for teaching the radiolabeling of a Fab'-PEG conjugate.

In response to the previous rejections, applicants have established that the combination of Zapata et al. and Braxton et al. does not make obvious the claims on which claims 34 and 35 depend. Dependent claims 34 and 35 are non-obvious for the same reason, accordingly, their rejection is believed to be misplaced and should be withdrawn.

20-21. Applicants note the provisional obviousness-type double patenting rejection over co-pending application Serial No. 09/355,014, and will be ready to file a Terminal Disclaimer, when allowable subject matter is indicated in either of these cases.

22. The present application and Application Serial No. 09/355,014 were subject to an obligation to assignment to the same entity, Genentech, Inc., at the time the present invention was made. The assignment in parallel Application Serial No. 09/355,014 has been recorded in the USPTO on January 16, 2001, under Reel/Frame: 011458/0859. The Assignment in the present case was recorded on May 20, 1999 under Reel 010021, Frame 0349.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 23, 2002

By: _____

Ginger R. Dreger
Registration No. 33,055
Attorney of Record
Customer No. 20,995
(415) 954-4114

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Once Amended) A conjugate consisting essentially of an antibody Fab' fragment, covalently attached to a polyethylene glycol (PEG) molecule having an average molecular weight of at least 20 kD, wherein the apparent size of the conjugate is at least about 500 kD, and at least about 8 fold greater than the apparent size of the antibody fragment.

~~2. [CANCEL] The conjugate of Claim 1, wherein the apparent size of the conjugate is at least about 800 kD.~~

~~3. [CANCEL] The conjugate of Claim 1, wherein the apparent size of the conjugate is at least about 1,400 kD.~~

~~4. [CANCEL] The conjugate of Claim 1, wherein the apparent size of the conjugate is at least about 1,800 kD.~~

~~5. [CANCEL] The conjugate of Claim 1, wherein the apparent size of the conjugate is at least about 8 fold greater than the apparent size of at least one antibody fragment.~~

~~6. [CANCEL] The conjugate of Claim 5, wherein the apparent size of the conjugate is at least about 15 fold greater than the apparent size of at least one antibody fragment.~~

~~7. [CANCEL] The conjugate of Claim 6, wherein the apparent size of the conjugate is at least about 25 fold greater than the apparent size of at least one antibody fragment.~~

~~8. [CANCEL] The conjugate of Claim 1, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and $F(ab')_2$.~~

~~9. [CANCEL] (Not Elected) The conjugate of Claim 8, wherein the antibody fragment is $F(ab')_2$.~~

~~10. [CANCEL] The conjugate of Claim 1, wherein at least one antibody fragment is covalently attached to no more than about 10 nonproteinaceous polymer molecules.~~

~~11. [CANCEL] The conjugate of Claim 10, wherein the antibody fragment is covalently attached to no more than about 5 nonproteinaceous polymer molecules.~~

~~12. [CANCEL] The conjugate of Claim 11, wherein the antibody fragment is covalently attached to no more than about 2 nonproteinaceous polymer molecules.~~

~~13. [CANCEL] The conjugate of Claim 12 wherein the antibody fragment is attached to no more than 1 nonproteinaceous polymer molecule.~~

~~14. [CANCEL] The conjugate of Claim 12, wherein the antibody fragment comprises a heavy chain and a light chain derived from a parental antibody, wherein in the parental antibody the heavy and light chains are covalently linked by a disulfide bond between a cysteine residue in the light chain and a cysteine residue in the heavy chain, wherein the antibody fragment the cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.~~

~~15. [CANCEL] The conjugate of Claim 8 wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH.~~

~~16. [CANCEL] The conjugate of Claim 15 wherein the antibody fragment is covalently attached to no more than 1 nonproteinaceous polymer molecule.~~

~~17. [CANCEL] The conjugate of Claim 16 wherein the nonproteinaceous polymer molecule in the conjugate is covalently attached to the hinge region of the antibody fragment.~~

~~18. [CANCEL] The conjugate of Claim 1 wherein at least one nonproteinaceous polymer is a polyethylene glycol (PEG).~~

~~19. [CANCEL] The conjugate of Claim 18 wherein the PEG has an average molecular weight of at least about 20 kD.~~

20. (Once Amended) The conjugate of Claim 1 wherein the PEG has an average molecular weight of at least about 40 kD.

~~21. [CANCEL] The conjugate of Claim 19 wherein the PEG is a single chain molecule.~~

~~22. [CANCEL] (Not Elected) The conjugate of Claim 20 wherein the PEG is a branched chain molecule.~~

~~23. [CANCEL] (Not Elected) The conjugate of Claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is a $F(ab')_2$ and is covalently attached to no more than about 2 PEG molecules.~~

24. ~~[CANCEL] The conjugate of Claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group~~

~~consisting of Fab, Fab' and Fab'-SH and is covalently attached to no more than one PEG molecule.~~

25. (Once Amended) The conjugate of Claim 1 wherein the PEG molecule is covalently attached to the hinge region of the antibody fragment.

26. (Once Amended) The conjugate of Claim 1 wherein the antibody fragment comprises an antigen binding site that binds to human interleukin-8 (IL-8).

~~27. [CANCEL] The conjugate of Claim 26, wherein the conjugate contains no more than one antibody fragment, wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH, wherein the antibody fragment is covalently attached to no more than one nonproteinaceous polymer molecule, and wherein the nonproteinaceous polymer molecule is a polyethylene glycol having an average molecule weight of at least about 30 kD.~~

28. The conjugate of Claim 26 wherein the antibody fragment comprising the anti-human IL-8 antigen binding site is humanized.

29. The conjugate of Claim 28 wherein the anti-human IL-8 antigen binding site comprises the complementarity determining regions of a light chain polypeptide amino acid sequence selected from the group consisting of the 6G4V11N35A light chain polypeptide amino acid sequence of Fig. 36 (SEQ ID NO:56) and the 6G4V11N35E light chain polypeptide amino acid sequence of Fig. 45 (SEQ ID NO:62).

~~30. [CANCEL] The conjugate of Claim 1 wherein the conjugate contains no more than one antibody fragment.~~

31. A composition comprising the conjugate of Claim 1 and a carrier.

32. The composition of Claim 31 that is sterile.

33. The conjugate of Claim 1, wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment and nonproteinaceous polymer molecules that form the conjugate.

34. The conjugate of Claim 1, wherein the covalent structure of the conjugate incorporates one or more nonproteinaceous labels, and wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment, nonproteinaceous polymer and nonproteinaceous label molecules that form the conjugate.

35. The conjugate of Claim 34 wherein at least one nonproteinaceous label is radiolabel.

36. (New) A conjugate consisting essentially of a Fab' fragment, attached to a single-chain polyethylene glycol (PEG) molecule of at least 20 kD, wherein said conjugate has an apparent size of at least about 500 kD and at least about 8 fold greater than the apparent size of at the antibody fragment.

W:\DOCS\GRD\GRD-9775.DOC
122002